(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 229 844 A1**

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(21) Application number: 86903594.9

(22) Date of filing: 12.06.86

Data of the international application taken as a basis:

(86) International application number: PCT/JP 86/00293

(87) International publication number: WO 86/07538 (31.12.86 86/28)

(51) Int. Cl.⁴: A 61 K 31/557, A 61 K 9/10

(30) Priority: 17.06.85 JP 129920/85

(43) Date of publication of application: 29.07.87 Bulletin 87/31

(84) Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

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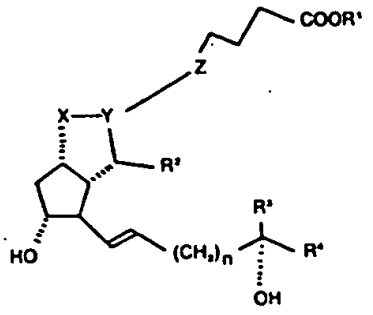
(54) FAT EMULSION OF PROSTAGLANDIN I 27.

(57) A fat emulsion containing a prostaglandin I_2 represented by the formula (I) wherein X represents an oxygen atom or a methine group, Y represents a carbon atom, and Z represents a methylene or methine group provided that, when X represents an oxygen atom, the Y–Z bond is a carbon-to-carbon double bond and, when X represents a methine group, the X–Y bond is a carbon-to-carbon double bond and Z represents a methylene group; R^1 represents a hydrogen atom or an alkyl group, R^2 represents a hydrogen or fluorine atom, R^3 represents a hydrogen atom, or a methyl, ethyl or vinyl group, R^4 represents a substituted or unsubstituted alkyl group containing 1 to 10 carbon atoms, a substituted or unsubstituted alkenyl group containing 2 to 10 carbon atoms, a substituted or unsubstituted alkynyl group containing 2 to 10 carbon atoms, or a substituted or unsubstituted cycloalkyl group containing 3 to 8 carbon atoms, and n represents 0 or 1.



(I)

EP 0 229 844 A1

Specification

Technical Field

This invention relates to fat emulsions containing the prostaglandin I_2's.

More particularly, it relates to new fat emulsions containing, as an active ingredient, the prostaglandin I_2's which are not only thrombolytic but are useful in the treatment of cardiovascular-renal system disorders as well.

Background of the Invention

The prostaglandins exibit a wide range of physiological activities and have been finding widespread medicinal applications because of their diverse and useful biological actions such as peripheral circulatory improvement, vasodilation, antiulceration, hypotensive, induction of labor, thrombolytic, and antiasthmatic. In recent years, these compounds have been studied for possible new indications such as anticancer, osteometabolism improvement, antiviral, hepatic protection, diuresis. In particular, the naturally occurring prostacyclin is a local hormone predominantly produced in vivo from the vascular wall of arteries; owing to its potent physiological effects such as platelet agglutination inhibitory activity and vasodilating activity, this local hormone is an important factor which regulates

in vivo cellular functions, and hence an attempt has been made to use the naturally occurring prostacyclin per se as a pharmaceutical product [P. J. Lewis, J. O. Grady et al., Clinical prostacyclin, Raven Press, N.Y. (1981)].

On the other hand, however, when these useful prostaglandins are applied as pharmaceutical products, various problems are encountered with respect to the in vivo instability inherent in the prostaglandins, side effects attributable to a wide range of their physiological effects, and the difficulties of formulations due to their chemical instability.

Thus, intensive studies have been carried out at home and abroad with regard to chemically stable synthetic prostacyclin derivatives comparable to naturally occurring prostacyclin in terms of biological actions.

Meanwhile, attempts have been made to stabilize chemically unstable prostacyclin in dosage form as well as to improve its drug efficacy. For example, propositions have been put forth regarding a method of stabilizing the prostacyclin as the clathrate compound using cyclodextrin (Joseph Scesitri et al., Japan Laid-Open Patent Showa 54-56685), a method of stabilizing the prostacyclin with surface active agents (Moo Yang Chou et al., Japan Laid-Open Patent Showa 55-15470), a pharmaceutical preparation by first obtaining a new ester derivative of prostacyclin with the higher fat solubility, emulsifying this ester derivative in a fat, and maintaining its activity comparable to that of the parent prostacyclin (Fukaya et al.,

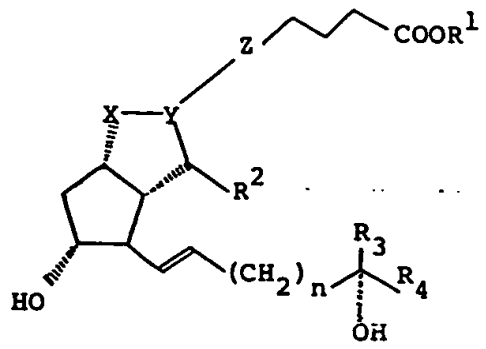
Japan Laid-Open Patent Showa 60-13779), and so forth.

The fat emulsions containing PGE_1 or PGA_1 have recently been proposed as the stabilized prostaglandin fat preparations which possess vasodilating, platelet agglutination inhibitory, and hypotensive activities [Mizushima et al., Japan Laid-Open Patent Showa 58-222014 and Japan Laid-Open Patent Showa 59-141518; and Mizushima et al., Ann. Rheum. Diseases, 41, 263 (1982); Pharm. Pharmacol., 35, 398 (1983)]. Such techniques are applied to the preparation of the anti-tumor agents; a proposal has been set forth with respect to the improvement of selective delivery of anticancer drugs to the target organ (Okamoto et al., Japan Laid-Open Patent Showa 59-122423).

Disclosure of the Invention

The inventors noticed the aforementioned facts and made intensive studies on some of the chemically stable synthetic prostaglandin I_2's in order to prolong their effects and enhance their clinical efficacy. As a consequence, we prepared said fat emulsion containing the stable prostaglandin I_2's, and discovered that the said preparations have attained these objects. The inventors, therefore, arrived at the present invention.

This invention, therefore, concerns the fat emulsions containing the prostaglandin I_2's expressed by the following formula (I):



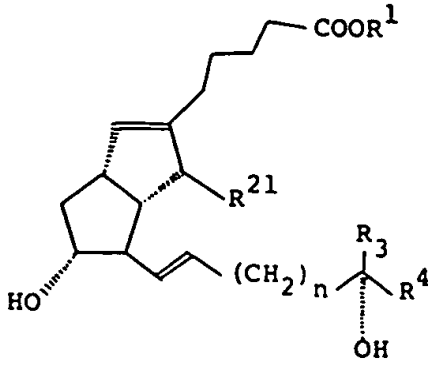
...(I)

where X represents an oxygen atom or a methine group, Y is a carbon atom, Z represents a methylene or methine group; when X is an oxygen atom, the mode of Y-Z binding is a double bond of carbon-carbon; and when X is a methine group, the mode of X-Y binding is a double bond of carbon-carbon and Z is a methylene group; R_1 represents a hydrogen atom or alkyl group, R_2 represents a hydrogen atom or fluorine atom, and R_3 represents a hydrogen atom, methyl group, ethyl group or vinyl group. R_4 represents a substituted or unsubstituted alkyl group with 1 - 10 carbon atoms, a substituted or unsubstituted alkenyl group with 2 - 10 carbons atoms, a substituted or unsubstituted alkynyl group with 2 - 10 carbon atoms, or a substituted or unsubstituted cycloalkyl group with 3 - 8 carbon atoms; and n is zero (0) or an integer of value 1.

The fat emulsions in the invention are new fat emulsions containing chemically stable prostaglandin I_2's; such fat emulsions possess longer duration of action, improve the stability of the prostaglandin I_2's, reduce manifestation of side effects, exhibit, at the same time, potent pharmacological effects, and are useful as the preparations for use in intravenous administration.

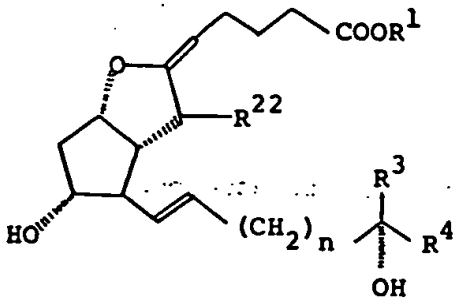
Most of the prostaglandin I_2's in the aforementioned formula (I) are the compounds known to be stabilized prostaglandin I_2's (Japan Laid-Open Patent Showa 58-150583, and Japan Laid-Open Patent Showa 57-32981).

In the aforementioned formula (I), X represents an oxygen atom or a methine group, Y is a carbon atom, Z represents a methylene or methine group; when X is an oxygen atom, the mode of Y-Z binding is a double bond of carbon-carbon, and when X is a methine group, the mode of X-Y binding is a double bond of carbon-carbon and Z is a methylene group. From these definitions, it is preferable in the present invention that the active ingredient is the isocarbacyclins expressed by the forllowing formula (Ia):



...(Ia)

(where R_1, R_3, R_4, and n are defined as above; R_{21} represents a hydrogen atom); or that the active ingredient is the 7-fluoro-prostacyclins expressed by the following formula (Ib):



...(Ib)

(where R_1, R_3, R_4, and n are defined as above; R_{22} represents a hydrogen atom).

In the aforementioned formula (1), R_1 is a hydrogen atom or alkyl group. The said alkyl group may be an alkyl group with 1 - 10 carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl, octyl, and decyl group. The R_1 is preferably a hydrogen atom or methyl group.

R_4 represents a substituted or unsubstituted alkyl group with 1 - 10 carbon atoms, a substituted or unsubstituted alkenyl group with 2 - 10 carbon atoms, a substituted or unsubstituted alkynyl group with 2 - 10 carbon atoms, or a substituted or unsubstituted cycloalkyl group with 3 - 10 carbon atoms. The unsubstituted alkyl group with 1 - 10 carbon atoms may, for example, be a methyl, propyl, butyl, pentyl, hexyl, octyl, decyl group, etc. The unsubstituted alkenyl group with 2 - 10 carbon atoms may, for example, be a vinyl, 2-propenyl, 3-butenyl,

2-pentenyl, 2-methyl-3-pentenyl, 2-hexenyl, 5-methyl-4-hexenyl, 2,6-dimethyl-5-heptenyl group, etc. The unsubstituted alkynyl group with 2 - 10 carbon atoms may, for example, be a 2-butynyl, 3-butynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 2-hexynyl, 4-hexynyl group, etc. The unsubstituted cycloalkyl group with 3 - 8 carbon atoms may, for example, be a cyclopropyl, cyclopentyl, cyclohexyl group, etc.

The substituent of these alkyl, alkenyl, alkynyl, and cycloalkyl groups may be such halogen atoms as fluorine and chlorine; such lower alkoxy groups as methoxy, ethoxy, propoxy, and butoxy group; a halogenoalkyl group such as trifluoromethyl; a substituted or unsubstituted phenoxy group which has been substituted or unsubstituted with a halogen atom or a lower alkoxy group; etc.

The prostaglandin I_2's in formula (1) may be prepared, for example, according to the methods described in Japan Laid-Open Patent Showa 58-150583 and Japan Laid-Open Patent Showa 57-32981.

The stable prostaglandin I_2's shown in the aforementioned formula (1) are specifically listed as follows:

(1) Isocarbacyclin

(2) 16,17,18,19,20-Pentanor-15-cyclopentylisocarbacyclin

(3) 16,17,18,19,20-Pentanor-15-cyclohexylisocarbacyclin

(4) 17,20-Dimethylisocarbacyclin

(5) 15-Deoxy-16-hydroxyisocarbacyclin

(6) 15-Deoxy-16-hydroxy-17,20-dimethylisocarbacyclin

(7) 7-Fluoroprostacyclin

(8) 7-Fluoro-16,17,18,19,20-pentanor-15-cyclopentylprostacyclin

(9) 7-Fluoro-16,17,18,19,20-pentanor-15-cyclohexylprostacyclin

(10) 7-Fluoro-17,20-dimethylprostacyclin

(11) 7-Fluoro-16,16-dimethylprostacyclin

(12) 7,16-Difluoroprostacyclin

(13) 15-Deoxy-16-hydroxy-7-fluoroprostacyclin

(14) 15-Deoxy-16-hydroxy-7,16-difluoro-prostacyclin

(15) The methyl esters of (1) - (14)

The fat emulsions in the invention comprises, as main constituents, the prostaglandin I_2's in formula (I), 5 - 50 w/v % of vegetable oil, 1 - 50 parts, preferably 5 - 30 parts, of phospholipid for 100 parts of the vegitable oil, and an appropriate quantity of water.

The vegetable oil may be soybean oil, cotton seed oil, sesami oil, safflor oil, and corn oil, but preferably soybean oil.

The soybean oil of choice is a refined soybean oil with high purity. Preferably, it is the highly purified, refined soybean oil obtained by further purifying common refined soybean oil by, for example, steam distillation.

The phospholipid is a purified phospholipid such as egg yolk lecithin and soybean lecithin. The phospholipid may be used which has been prepared by fractionation using an organic solvent according to a conventional method, that is, by slowly adding, with stirring, acetone to a crude yolk phospholipid dissolved in a cold n-hexane-acetone mixture, collecting insolubles by filtration, repeating the procedure

of dissolution, followed by precipitation, and finally removing the solvent by distillation. The product comprises, as main constituents, phosphatidylcholine and phosphatidylethanolamine. The other phospholipids may be phosphatidyl-inositol, phosphatidylserine, sphingomyelin, etc.

To the fat emulsions in the invention may, where necessary, be further added an emulsifying adjuvant, stabilizer, high molecular substance, isotonizing agent, etc.

The emulsifying adjuvant may, for example, be up to 0.3 w/v % of fatty acids with 6 - 22, preferably 12 - 20, carbon atoms or their pharmaceutically acceptable salts, and so on. Either of the fatty acids with 6 - 22 carbon atoms may be used if they can be added to pharmaceutical products. Such fatty acids are either of the straight or of the branched chain; they are preferably stearic, oleic, linolic, palmitic, linolenic, and myristic acids. These salts may be salts with alkali metals such as sodium and potassium, with alkaline earth metals such as calcium, and so on.

The stabilizing agent may, for example, be less than 0.5 w/v %, preferably less than 0.1 w/v %, of the cholesterols, less than 5 w/v %, preferably less than 1 w/v %, of phosphatidic acids, and so forth.

The high molecular substances may, for example, be 0.1 - 5 parts by weight, preferably 0.5 - 1 part by weight, of albumin, dextran, vinyl polymers, nonionic surface active agents, gelatin, hydroxyethyl starch, etc. for 1 part by weight of the prostaglandin I_2's.

The albumin may preferably be of human

origin, and the vinyl polymers may be polyvinylpyrrolidone, etc. The nonionic surface active agents may, for example, be polyalkylene glycols, polyoxyalkylene copolymers, the polyoxyalkylene derivatives of hardened castor oil, the polyoxyalkylene derivatives of castor oil, etc.

The content of the prostaglandin I_2's in the fat emulsions may be suitably increased or decreased according to the form of the emulsions and applications; in general, minute quantities, for example, 1.0 mg - 0.2 µg/ml in the fat emulsions are sufficient.

The fat emulsions in the present invention are prepared, for example, in the following manner: Predetermined amounts of vegetable oil, phospholipid, the prostaglandin I_2's, and other additives are mixed and the mixture is warmed to a solution. The solution is homogenized by, for example, the use of a homogenizer of the high-pressure jet type, an ultrasonic homogenizer, etc. The homogenate is further homogenized following the addition of a necessary amount of water in order to prepare the fat emulsions in the invention. Under preparatory conditions, the additives such as a stabilizer and isotonizing agent may be added after the fat emulsions have been formed.

The fat emulsions may be administered parenterally such as by injection, most preferably intravenously. For instance, the prostaglandin I_2's are administered intravenously by continuous infusion once a day in dose levels of 0.01 - 0.1 µg/kg, or 0.01-0.1 ng/kg/min. The fat emulsions in the present invention possess very potent effects, are long-acting by sustained release and selective for lesions; therefore,

administration of small doses enables effective treatment.

Since intravenous administration is possible, rapid onset of action can be anticipated, drug efficacy is consistent, and since doses are small, there is less manifestation of side effects.

Furthermore, the particles are extremely minute, and the average size of them is less than 1.0 μ. The safety (stability) during storage is very good.

Best Manner to Implement the Invention

Using the following Examples, the best methodologies to embody the present invention are described below:

Example 1

Preparation of a fat emulsion containing isocarbacyclin (compound I)

To 10 g of a refined soybean oil were added 1.2 g of egg yolk lecithin and 1000 μg of isocarbacyclin. The mixture was heated at 60 - 80°C to a solution. To this solution were added 50 ml of distilled water and then 2.5 g of glycerol. Distilled water for injection was added to make the solution to 100 ml. The solution was roughly emulsified in a homomixer.

Using a Manton-Gaulin homogenizer, the crude emulsion was then further emulsified by passing 10 times through the instrument under a first-stage pressure of 120 kg/cm^2 and a total pressure of 500 kg/cm^2. There was obtained a homogenized, finely dispersed, 10 % soybean oil-containing fat

emulsion which contained isocarbacyclin (compound I) in a final concentration of 10 µg/ml.

Example 2

Preparation of the fat emulsions, each of which contained 16,17,18,19,20-pentanor-15-pentylisocarbacyclin (compound II), 7-fluoro-16,17,18,19,20-pentanor-15-cyclopentylprostacyclin methyl ester (compound III), and isocarbacyclin methyl ester (compound IV), respectively

Using compounds II, III, and IV, the 10% soybean oil-containing fat emulsions were prepared in the same manner as in Example 1, each of which contained the above-mentioned compound respectively, in a final concentration of 5 µg/ml, 5 µg/ml, and 10 µg/ml, respectively.

Examples 5 - 16

Evaluation of drug activities using human platelets

The time course of the formation of cyclic AMP by the fat emulsion in the invention was determined using human platelets so as to compare with the time course of the compound which was not emulsified in fat. Human blood 50 ml was collected using 1 part of 3.8 % sodium citrate for 9 parts of blood. The blood sample was centrifuged at 1300 rpm for 10 minutes. The upper layer was taken out as PRP (platelet-rich plasma) and centrifuged at 3000 rpm for 20 minutes. The precipitate thus obtained (platelets) was suspended in 2 ml of Tris buffered solution-saline-glucose-EDTA (TSG-EDTA) (pH 7.4).

The fat emulsion, which had previously been

transferred in a plastic tube containing 350 µl of TSG-EDTA and 50 µl of platelet suspension and incubated at 37°C, was supplemented with 50 µl of 5mM isobutylmethylxanthin dissolved in saline, and 2 minutes later, reactions were stopped with 0.5 ml of 10% trichloroacetic acid (TCA). The cells were destroyed by thawing the lyophilized specimen in order to release intracellular cyclic AMP. After removal of TCA with water-saturated ether, the content of C-AMP was determined by radio immunoassay technique.

The results are summarized in Table 1. As is clear from these results, it was demonstrated that the production capability of C-AMP by the fat emulsion was satisfactorily maintained over time.

Table 1. Production capability and maintenance of cyclic AMP by fat emulsions

Examples	Compounds	Time (min.)	C-AMP production (pico mol)	Relative value (%)
Example 5	Fat emulsion (I)	0	80	100
" 6	" "	30	100	125
" 7	" "	60	100	125
Comparison 1	Compound (I)	0	320	100
" 2	" "	30	200	63
" 3	" "	60	100	31

Examples	Compounds	Time (min.)	C-AMP production (pico mol)	Relative Value (%)
Example 8	Fat emulsion (II)	10	130	100
" 9	" "	30	190	146
" 10	" "	60	100	76
Comparison 4	Compound (II)	10	430	100
" 5	" "	30	320	74
" 6	" "	60	120	27
Example 11	Fat emulsion (III)	30	55	100
" 12	" "	60	30	55
" 13	" "	120	30	55
Comparison 7	Compound (III)	30	100	100
" 8	" "	60	90	90
" 9	" "	120	40	40
Example 14	Fat emulsion (IV)	30	40	100
" 15	" "	30	45	111
" 16	" "	120	28	70

Example 17

Determination of platelet agglutination inhibitory action

Fifty (50) µl of the fat emulsion obtained in Examples 1 and 2 was transferred into 950 µl of saline or 2 % bovine serum albumin (BSA) and incubated at 37°C for 1, 3, and 10 minutes. Next, the ADP platelet agglutination inhibitory action by PRP was determined using the filtrate which had been passed through a 0.025 µm filter. A known quantity of the dilution before filtration was added to PRP and incubated at 37°C for 1 minute. Thereafter, ADP agglutination was induced to construct a dose-response curve. The platelet agglutination inhibitory action was calculated from this curve. The results are presented in Table 2.

Table 2. Platelet agglutination inhibitory action

Conditions		Platelet agglutination inhibitory action (%)			
Dilutions	Incubation time (min.)	Fat elulsion (IV)	Compound (IV)	Fat emulsion (I)	Compound (I)
2 % BSA	1	13.7	65.4	87.5	100.1
	3	23.1	NT	83.5	NT
	10	27.1	56.2	90.6	107.7
Saline	10	-	-	14.1	41.1

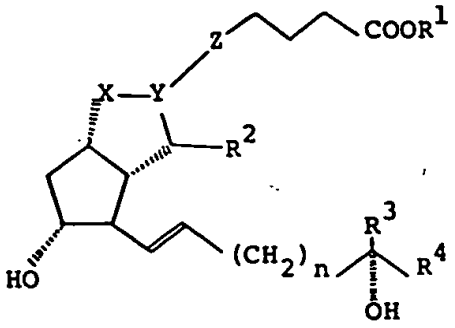
As indicated in Table 2, in the fat emulsions in the present invention, the active ingredient of the prostaglandin I_2's is gradually released, and thus these dosage forms provide a sustained-release delivery.

Potential applications in industry

The fat emulsions containing the prostaglandin I_2's in the present invention possess potent effects, provide a sustained-release delivery, and are selective for lesions. Therefore, they can provide effective therapy in small doses and are extremely useful in the treatment of various kinds of cardiovascular diseases such as thrombotic diseases.

Claims

1. The fat emulsions containing the prostaglandin I_2's expressed by the following formula (I):



...(I)

where X represents an oxygen atom or a methine group, Y is a carbon atom, Z represents a methylene or methine group; when X is an oxygen atom, the mode of Y-Z binding is a double bond of carbon-carbon, and when X is a methine group, the mode of X-Y binding is a double bond of carbon-carbon and Z is a methylene group; R_1 represents a hydrogen atom or alkyl group, R_2 represents a hydrogen atom or fluorine atom, and R_3 represents a hydrogen atom, methyl group, ethyl group or vinyl group. R_4 represents a substituted or unsubstituted alkyl group with 1 - 10 carbon atoms, a substituted or unsubstituted alkenyl group with 2 - 10 carbon atoms, a substituted or unsubstituted alkynyl group with 2 - 10 carbon atoms, or a substituted or unsubstituted cyclo-alkyl group with 3 - 8 carbon atoms; and n is zero (0) or an integer of value 1.

2. The fat emulsions containing the prostaglandin I_2's described in Claim 1 wherein the prostaglandin

I_2's expressed by formula (I) are the iso-carbacyclins or their alkyl esters.

3. The fat emulsions containing the prostaglandin I_2's described in Claim 1 wherein the prostaglandin I_2's expressed by formula (I) are the 7-fluoro-prostacyclins or their alkyl esters.

INTERNATIONAL SEARCH REPORT 0229844

International Application No. PCT/JP86/00293

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl[4] A61K31/557, A61K9/10

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC	A61K31/557, A61K9/10

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category*	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	JP, A, 59-210044 (Teijin Limited) 28 November 1984 (28. 11. 84) Pages 1 and 10 (Family: none)	1 - 2
Y	JP, A, 60-13779 (The Green Cross Corp.) 24 January 1985 (24. 01. 85) Pages 1, 3 and 5 (Family: none)	1 - 3
Y	JP, A, 54-110313 (Sandoz A.G.) 29 August 1979 (29. 08. 79) Pages 1 to 3 & DE, A, 2900428 & GB, A, 2012168	1 - 3
A	JP, A, 58-203911 (Ono Yakuhin Kogyo Kabushiki Kaisha) 28 November 1983 (28. 11. 83) Page 7 & DE, A, 3318571 & US, A, 4503068	1 - 3
A	JP, A, 53-50141 (Ono Yakuhin Kogyo Kabushiki Kaisha) 8 May 1978 (08. 05. 78) Page 1 (Family: none)	1 - 3

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [9]
August 25, 1986 (25. 08. 86)	September 8, 1986 (08. 09. 86)
International Searching Authority [1]	**Signature of Authorized Officer [20]**
Japanese Patent Office	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

P	JP, A, 61-44819 (Zaidan Hojin Sagami Chuo Kagaku Kenkyusho, Mitsubishi Yuka Yakuhin Kabushiki Kaisha) 4 March 1986 (04. 03. 86) Page 4 (Family: none)	1 - 2
P	JP, A, 60-260524 (Sekimoto Hiroshi, Akiyoshi Masataka) 23 December 1985 (23. 12. 85) Page 1, (Family: none)	1 - 3
P	JP, A, 60-243079 (Asahi Glass Co., Ltd.) 3 December 1985 (03. 12. 85)	1, 3

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE[10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers..... because they relate to subject matter[12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out[13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING[11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International Application No. 0229814 PCT/JP86/00293

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	Page 4 (Family: none)	
P	JP, A, 60-169430 (Teijin Limited) 2 September 1985 (02. 09. 85) (Family: none)	1, 3
P	JP, A, 60-149524 (The Green Cross Corp.) 7 August 1985 (07. 08. 85) (Family: none)	1 - 3

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

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2. ☐ Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [12], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [13]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.